Claim 1 requires:

a) a concentrated lipase of *Rhizopus delemar*,

b) a neutral protease of *Aspergillus melleus*, and

c) an amylase of *Aspergillus oryzae*.

The cited references do not satisfy a finding of *prima facie* obviousness as the cited art does not teach or suggest all the claim limitations and there is no teaching or suggestion to one of ordinary skill in the art to combine Sipos and Ogawa et al. The Office Action asserts that Sipos would teach pharmaceutical compositions for treating digestive disorders comprising lipase of Rhizopus delemar and amylase of *Aspergillus oryzae*. This is simply not the case. Sipos merely discloses glycerol ester hydrolase (a lipase), a general type of enzyme which is classified as being "3.1.1.3" according to the Enzyme classification system (EC) as proposed by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB). Clearly this is not a teaching of a lipase of *Rhizopus delemar*. At best, Sipos teaches a broad genus that might include the claimed species. The conclusion put forth in the Office Action that the "lipases" as disclosed by Sipos and the specific microbial lipases as provided by the present invention are the same appears to be based on a misunderstanding of the EC nomenclature system. The EC nomenclature system for enzymes as provided by NC-IUBMB only classifies enzymes according to the general chemical reaction which they catalyze. Therefore, the entry "E.C 3.1.1.3" refers quite generally to "triacylglycerol lipases" which catalyze reactions of the type "triacylglycerol $+H_2O=$ diacylglycerol + a carboxylate." Thus, the EC classification provides a very broad generic group of enzymes which may vary dramatically in their individual origins and/or properties like pH stabilities, activity profiles, compatibilities with other enzymes like proteases, etc. Thus, this teaching of such a broad and heterogeneous genus like the "E.C. 3.1.1.3" group of triacylglycerol lipases does not provide disclosure of the species of lipase

of Rhizopus. Furthermore, it is expressly stated in the Sipos reference (cf. col 6, lines 22 - 26) that the disclosed enzymes are in fact typically derived from animal sources. Thus, the Sipos reference teaches away from the instant invention as the enzymes of the present invention are derived from microorganisms. It is important to note in this context, that enzymes from microorganism sources are an essential feature of the present invention, because it is normally very difficult to achieve very high specific enzymatic activities per dose with digestive enzymes from animal sources. In particular, the lipase of *Rhizopus delemar* is well suited for the purpose of the instant invention due to its favorable properties as outlined in the specification and due to its relative compatibility with the other ingredients of the enzyme mixture of the present invention. Sipos simply does not teach the lipase of *Rhizopus delemar* as claimed.

Applicants further submit that the Office Action's assertion that Sipos discloses an amylase from *Aspergillus oryzae* is in error for reasons similar to those stated above. In column 6, lines 11-12, Sipos mentions that the principal active enzymes of his compositions would include, among others, "alpha-Amylase E.C. 3.2.1.1". The amylase of *Aspergillus oryzae* as used in the enzyme mixture of the present invention is also said to be an amylase of the "E.C. 3.2.1.1"- type. Again, the Office Action's conclusion that the "amylases" as disclosed by Sipos and the specific microbial amylases as provided by the present invention are the same seems to be based on a misconception of the EC nomenclature system. The entry "E.C. 3.2.1.1" refers to "alpha-amylase" which quite generally catalyze the endohydrolysis of 1,4-α-D-glucosidic linkages in polysaccharides containing three or more 1,4-α-linked D-glucose units. The EC classification at best provides a very broad generic group of enzymes which may dramatically vary in their individual origins and/or properties like pH stability, activity profiles, and compatibilities with other enzymes like proteases, etc. Thus, this teaching of such a broad and heterogeneous genus like the "E.C. 3.2.1.1" group of amylases does not provide disclosure of the species of amylase of *Aspergillus*. Applicants

respectfully note that the amylase of *Aspergillus oryzae* is particularly suited for the purposes of the present invention due to its favorable properties as discussed in the specification and due to its relative compatibility with the other ingredients of the enzyme mixture of the present invention. The exact source of a specific enzyme is critical since enzymes from different organisms often vary dramatically in their properties. Sipos merely teaches that amylases classified as "EC 3.2.1.1." are suitable for the disclosed composition. Sipos does not teach the amylase of *Aspergillus oryzae* as claimed.

Applicants respectfully submit that a thorough reading of Sipos reveals that using digestive enzymes from mammalian pancreatic extracts of hog, bovine or sheep origin results in certain drawbacks which need to be overcome. For example, one such drawback is the poor acid stability of pancreatic enzymes (see Sipos col. 1, lines 38-45). Another drawback is the insufficiency of bile acid and buffering capacity in the small intestine (see Sipos, col. 2, lines 64-67). As a solution to these problems, Sipos proposes an improved coating and/or the addition of a buffer (see Sipos col. 1, lines 14-18, lines 27-32 and claims). In contrast, the present invention does not propose to use enteric coated pharmaceutical compositions of mammalian pancreatic digestive enzyme extracts which contain an excess of buffer substance, but instead proposes to use a carefully selected and adjusted mixture of three specific enzymes (a lipase, a protease, and amylase), each of microbial origin. These microbial enzymes may be administered without any coating because they are distinguished over pancreatic enzymes of mammalian origin by an improved acid stability (specification pg. 6).

Further, the present invention provides mixtures of enzymes which while having high specific activity of the substitution enzymes contained therein permit use of relatively low dosage quantities (specification pg. 5). This contrasts with the approach taught in Sipos wherein compositions having

reduced levels of digestive enzymes are used in order to circumvent certain side effects. (see Sipos col. 1, lines 15-19).

As stated previously, the Sipos compositions require the presence of 15 to about 60 % w/w of a buffering agent (see Sipos, col 7, lines 7 - 8). The presence of buffering agents reduces the concentration of therapeutically active enzymes and results in a lowered amount of therapeutically active digestive enzymes being available per dosage form. In contrast, an object of the present invention is to provide mixtures of digestive enzymes with a high enzymatic activity which permit the use of relatively low dosage quantities. This object is not compatible with a Sipos-type composition, containing high quantities of buffer substances without enzymatic activity. Accordingly, one of skill in the art would not be inclined to look to Sipos for teachings relevant to achieving high enzymatic activity with low dosages. The Office Action's assertion that the above arguments are not commensurate in scope with the claims is misplaced. The presence or absence of buffering agents is discussed as it pertains to why a person of ordinary skill in the art would or would not consider modifying the teaching of the prior art to arrive a the present invention. The argument is merely presented to explain why the correct interpretation of the Sipos reference's teachings would lead away from the claimed invention.

The Ogawa et al. reference does not cure the deficiencies of the Sipos reference. Ogawa et al. teach a medicament comprising a histamine HZ receptor antagonist and/or a proton pump inhibitor, and a digestive enzyme. This composition is therefore different from the composition of the present invention. While the Ogawa reference mentions, among other proteases, the protease which is part of the instant invention, there is no teaching or suggestion to combine this protease with any other enzymes to provide an improved medicament for the treatment of digestive enzyme insufficiency and substitute endogenous lipolytic, proteolytic and amylotic activity. Thus, a person skilled in the art would not

have any motivation to combine the teachings of Ogawa et al. and of Sipos so as to arrive at the present invention.

Applicants maintain that in the field of enzyme compositions, it is never a routine task to simply interchange one enzyme (e.g. a protease) of a balanced mixture of enzymes with an arbitrarily selected other enzyme thought to have similar activity, particularly when the enzymes in question are isolated from organisms that are as disparate as mammals and microorganisms. The new enzyme must fulfill specific requirements, in particular being compatible with the other constituents of the mixture of enzymes and/or with endogenous active substances. One of ordinary skill in the art would not reasonably expect enzymes isolated from different organisms to have identical properties. In the present instance, there does not appear to be any suggestion or motivation provided for a person of skill in the art to try to modify Sipos to provide for the claimed enzymes and then to try to combine it with the teachings of Ogawa et al. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this Reply or the application in general, a telephone call to the undersigned at (202) 624-2845 would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and

please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #029300.52497US).

Respectfully submitted,

September 6, 2005

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